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Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data

Wendy Y Craig, Glenn E Palomaki, James E Haddow

Abstract

To examine the association between cigarette smoking in adults and serum lipid and lipoprotein concentrations the results of 54 published studies were analysed. Overall, smokers had significantly higher serum concentrations of cholesterol (3·0%), triglycerides (9·1%), very low density lipoprotein cholesterol (10·4%), and low density lipoprotein cholesterol (1·7%) and lower serum concentrations of high density lipoprotein cholesterol (−5·7%) and apolipoprotein AI (−4·2%) compared with non-smokers. Among non-smokers and light, moderate, and heavy smokers a significant dose response effect was present for cholesterol (0, 1·8, 4·3, and 4·5% respectively), triglycerides (0, 10·7, 11·5, and 18·0%), very low density lipoprotein cholesterol (0, 7·2, 44·4, and 39·0%), low density lipoprotein cholesterol (0, −1·1, 1·4, and 11·0%), high density lipoprotein cholesterol (0, −4·6, −6·3, and −8·9%), and apolipoprotein AI (0, −3·7 and −5·7% in non-smokers and light and heavy smokers).

These dose response effects may provide new evidence for a causal relation between exposure to cigarette smoke and changes in serum lipid and lipoprotein concentrations whether as a direct result of physiological changes or of dietary changes induced by smoking. Adequate prospective data to estimate the excess risk of coronary artery disease existed only for cholesterol concentration. When that information was combined with data from the present study, and given that smokers as a group face an average overall excess risk of coronary artery disease of 70%, it was estimated that the observed increased serum cholesterol concentration in smokers may account for at least 9% of that excess risk. Furthermore, the dose response effect of smoking on serum cholesterol concentration suggests a gradient of increased absolute risk of coronary artery disease between light and heavy smokers.

Foundation for Blood Research, PO Box 190, Scarborough, ME 04074, United States
Wendy Y Craig, PHD, *research scientist*
Glenn E Palomaki, BS, *director, division of biometry*
James E Haddow, MD, *vice president*

Correspondence to: Dr Haddow.

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Introduction

Cigarette smokers have a higher risk of coronary artery disease than non-smokers. Several possible explanations have been offered for this association, including altered blood coagulation,[1] impaired integrity of the arterial wall,[2] and changes in blood lipid and lipoprotein concentrations.[1 2] We examined the last of these explanations by analysing the extent to which published data support a relation between smoking and altered serum lipid and lipoprotein concentrations in adults.[3-56] We then used information from this analysis to estimate the excess risk of coronary artery disease associated with smoking that may be accounted for by changes in serum cholesterol concentrations.

Methods

DATA COLLECTION

Articles relating to the effects of long term cigarette smoking on serum concentrations of cholesterol, triglycerides, very low density lipoprotein cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and apolipoprotein AI in adults were identified by using the Medline search facility (1966-87) and the database of the Office on Smoking and Health (United States Department of Health and Human Services, Rockville, Maryland). The reference lists of these articles were then reviewed to identify additional studies. Data from these sources were grouped into the following categories as defined by the original authors: non-smokers, all current smokers, and light, moderate, and heavy current smokers. In most studies lipid concentrations were not adjusted by the original authors for variations in age, sex, weight, alcohol consumption, or physical activity. Several, however, were adjusted for one or more of these variables.[11 15 24 25 28 30 31 34 40 49 52] Three of these studies provided both adjusted and unadjusted data, and there was no qualitative difference between the two.[15 24 25] A fourth study presented unadjusted data but reported that adjustment did not affect the results.[55] For these reasons we did not make distinctions according to age, sex, or other population variables in the present analysis. When population subgroups other than groups exposed to cigarette smoke were reported we calculated a weighted mean for each available variable and used this value in the analysis.

Mass unit data were required for the present analysis so those studies in which the data were reported solely in the form of regression coefficients were excluded. Eleven of the studies included in this analysis presented data in terms of mass units and as regression coefficients. Such data were available for all of the variables discussed in the present report with the exception of very low density lipoprotein cholesterol; in each case the conclusions drawn did not differ between the two methods of analysis. We also excluded studies that contained insufficient data for analysis, such as those that omitted the number of subjects in each category of smoking and those that investigated ex-smokers, pipe or cigar smokers, or the short term effects of smoking.

DATA ANALYSIS

The means and standard deviations for each of the lipid and lipoprotein variables were expressed in mmol/l; when necessary the reported values were converted into SI units (1 mmol/l=88·6 mg/100 ml for triglycerides and 38·7 mg/100 ml for cholesterol[57]). In studies in which the standard deviation was not provided for a given variable it was estimated from the pooled variance for that variable obtained from the studies in which standard deviations were provided. A large number of such estimated variances in a given set of data could result in a biased estimation of the actual variance. For each variable we examined the extent of this possible bias by comparing the overall pooled variance with and without the estimated standard deviations. The maximum difference in pooled standard deviation was 3·8%, and this difference did not materially affect the results.

Because of variability between studies in both the mean and the standard deviation of any given variable the data from each study were converted to a form suitable for comparison with other studies by calculating a Z score. This is the difference between smokers and non-smokers divided by the pooled standard deviation for each variable in a given study. The pooled standard deviation was used as the variance of a given non-smoking group did not always equal that of the corresponding smoking group. To estimate the overall effect of smoking we calculated a mean of the Z scores weighted by the reciprocal of the pooled standard error squared for each study to take into account differing sizes of samples and variabilities of assays. The weighted mean Z scores were tested for significance by Student's *t* test. The mean percentage difference in a variable between smokers and non-smokers was determined by multiplying the weighted mean Z score by the overall pooled standard deviation. To test for a dose response effect based on degree of exposure to cigarettes we performed a weighted linear regression between the four categories of smoking and the weighted mean Z score for each variable. The appendix describes the mathematical methods used.

Results

Table I gives the sources of data for the analyses and identifies whether a given study investigated smokers as a single group (all current smokers), as subgroups of exposure to cigarette smoke (dose response studies), or both. In addition, the lipid and lipoprotein analyses carried out in each study are given. Most studies dealt with serum cholesterol, triglyceride, and high density lipoprotein cholesterol concentrations; very low density lipoprotein cholesterol, low density lipoprotein

TABLE I—*Cigarette smoking and serum lipid and lipoprotein concentrations: summary of data available for present analysis*

Reference	All Smokers	Dose response	Comments	Total cholesterol	Triglycerides	Very low density lipoprotein cholesterol	Low density lipoprotein cholesterol	High density lipoprotein cholesterol	Apolipoprotein AI
3		X	*†	X					
4	X		*					X	
5	X	X	†					X	X
6	X	X							X
7		X		X	X				
8		X	*†	X					
9	X		*	X					
10		X						X	
11	X	X		X	X	X	X	X	
12		X	†	X					
13	X			X				X	
14	X		†					X	
15		X	*†					X	
16	X		†	X					
17	X	X	*†	X					
18		X		X	X				X
19		X	†					X	X
20		X	†		X			X	
21	X		†					X	X
22	X		*	X	X			X	
23	X		†	X				X	
24	X	X		X	X			X	
25		X	*†					X	
26		X	*†	X					
27	X	X	*	X				X	
28		X						X	
29	X		*†	X	X	X	X	X	
30	X		*†	X					
31	X	X	*	X					
32		X		X					
33		X	*	X	X				
34		X		X	X				
35	X		†	X					
36	X	X		X					
37		X		X				X	
38	X			X	X			X	
39	X							X	
40		X		X	X			X	
41	X	X		X	X	X	X	X	
42		X	*	X					
43		X		X	X				
44	X			X	X			X	
45	X			X	X	X	X	X	
46	X			X	X	X	X	X	
47	X	X	†		X		X		
48		X	*	X	X		X	X	
49	X		†		X			X	X
50		X	*	X	X			X	
51	X	X	†	X				X	
52	X		†					X	
53		X	*	X					
54	X	X		X	X			X	
55		X						X	
56	X		†	X	X			X	

*=SD not reported and estimated with pooled variance of remaining studies.
†=Value(s) reported as weighted average of subgroups.

TABLE II—*Classification of exposure among cigarette smokers, as defined in various published studies*

Reference	Category of smoking (No of cigarettes/day)		
	Light	Moderate	Heavy
8, 17, 18, 24, 25, 26, 27, 31, 34, 37, 42, 47, 48, 53, 55	1-9	10-19	≥20
7, 11, 33, 51, 54	1-14	15-24	≥25
6, 28, 36*	1-9		≥10
5, 15, 20, 32, 41, 50*	1-19		≥20
19, 40, 43*	1-14		≥15
12*			Heavy
3	5-10	20	≥30
10	<20	20	≥30

*One or more categories not defined in these studies.

TABLE III—*Serum cholesterol concentrations in non-smoking and smoking adults: analysis of published data**

Reference†	No of subjects in study (non-smokers/smokers)	Mean (SD) serum cholesterol (mmol/l)		% Change Z Score‡	in smokers§
		Non-smokers	All smokers		
9	519/576	6·28 (1·05)	6·49 (1·12)	0·193¶	3·3
11	218/113	4·94 (0·90)	5·09 (0·96)	0·168	3·1
13	149/242	4·07 (0·85)	4·19 (0·92)	0·137	3·0
16	3016/5741	5·51 (1·05)	5·67 (1·02)	0·154	2·9
17	280/1463	5·73 (1·05)	5·86 (1·12)	0·114	2·2
22	7/7	4·40 (1·05)	4·94 (1·12)	0·503	12·5
23	252/78	6·08 (0·89)	6·16 (1·11)	0·099	1·5
24	1023/809	6·56 (1·18)	6·67 (1·17)	0·076	1·7
27	3109/4995	5·35 (0·98)	5·43 (1·06)	0·075	0·5
29	91/75	5·39 (1·05)	5·61 (1·12)	0·205	4·1
30	1799/2336	5·43 (1·05)	5·49 (1·12)	0·057	1·1
31	3437/7571	6·54 (1·05)	6·95 (1·12)	0·352	5·9
35	165/360	5·75 (1·13)	6·41 (1·31)	0·526	11·5
36	18/23	6·42 (0·85)	6·86 (1·04)	0·460	6·9
38	74/37	5·15 (0·98)	5·14 (0·90)	−0·005	−0·1
41	43/43	5·22 (0·78)	5·57 (1·06)	0·398	6·7
44	10/10	4·31 (0·55)	4·62 (0·92)	0·410	7·2
45	3975/2434	5·56 (1·01)	5·63 (1·03)	0·076	1·4
46	38/53	5·59 (0·35)	5·65 (0·34)	0·197	1·2
51	761/392	6·34 (1·41)	6·37 (1·50)	0·024	1·5
54	93/98	4·89 (0·72)	5·09 (0·99)	0·235	4·2
56	22/20	4·37 (0·70)	4·68 (0·61)	0·473	7·2

*See appendix for description of calculations.
†Studies giving information on serum cholesterol concentrations in all current smokers *v* non-smokers.
‡Overall mean Z score 0·164 (95% confidence interval 0·148 to 0·180). Significant difference between smokers and non-smokers p<0·001.
§Overall mean percentage change in smokers 3·0% (95% confidence interval 2·7 to 3·3), p<0·001.
¶For example, 0·193 (Z score)=0·21 (cholesterol concentration in smokers minus concentration in non-smokers) divided by 1·09 (pooled SD).

TABLE IV—*Serum lipid and lipoprotein concentrations in non-smoking and smoking adults: analysis of published data*

Variable	All smokers		
	No of studies	Mean (SE) Z score*	% Difference from values in non-smokers*
Total cholesterol	22	0·163 (0·010)†	3·0
Triglycerides	13	0·139 (0·020)†	9·1
Very low density lipoprotein cholesterol	5	0·142 (0·024)†	10·4
Low density lipoprotein cholesterol	6	0·069 (0·024)†	1·7
High density lipoprotein cholesterol	22	−0·234 (0·013)†	−5·7
Apolipoprotein AI	4	−0·246 (0·029)†	−4·2

*See appendix for description of calculations.
†Significant difference between smokers and non-smokers p<0·001 by Student's *t* test.

cholesterol, and apolipoprotein AI concentrations were studied less often. The table also describes whether the data had to be modified before we could use them. Table II shows the different schemes of classifying smokers used in those studies that addressed the dose response effects of smoking.

Table III compares serum cholesterol concentrations in non-smokers and all current smokers to provide a detailed example of the type of analysis that we carried out for all the lipid variables in each non-smoking or smoking group. Serum cholesterol concentrations were higher in smokers in all but one study, leading to a significant overall increase of 3·0% (p<0·001).

Table IV summarises the effects of smoking on all the serum lipid and lipoprotein variables with the statistical methodology detailed for cholesterol in table III. Smoking was associated with significantly higher cholesterol, triglyceride, very low density lipoprotein cholesterol, and low density lipoprotein cholesterol concentrations and significantly lower high density lipoprotein cholesterol and apolipoprotein AI concentrations (all p <0·001).

Table V summarises the dose response effects of smoking on serum lipid and lipoprotein concentrations. Varying numbers of studies were included in the different dose response categories as some studies, for example, reported the effect of only light and heavy smoking (table II). The Z score for each variable in each category of smoking was significantly different from that in non-smokers except for very low density lipoprotein cholesterol and low density lipoprotein cholesterol concentrations in light smokers and low density lipoprotein cholesterol concentrations in moderate smokers. Cholesterol, triglyceride, very low density lipoprotein cholesterol, and low density lipoprotein cholesterol concentrations all showed a significant positive linear trend (p<0·001), whereas high density lipoprotein cholesterol and apolipoprotein AI concentrations showed a significant negative linear trend (p<0·001).

Discussion

Several studies have shown an association between cigarette smoking and altered serum lipid and lipoprotein concentrations, but many of these have lacked enough statistical power to establish a firm association. By combining the results of individual studies in the present analysis we have shown conclusively that smoking is associated with significantly higher serum concentrations of total cholesterol, triglycerides, very low density lipoprotein cholesterol, and low density lipoprotein cholesterol and lower serum concentrations of high density lipoprotein cholesterol and apolipoprotein AI and that this association is dose dependent.

To our knowledge the data relevant to changes in serum lipid and lipoprotein concentrations associated with degree of exposure to cigarette smoke have not previously been compiled and reviewed. The dose dependent relation that we found may provide new evidence for a causal relation. Because of personality or

TABLE V—*Effect of different exposures to cigarette smoke on serum lipid and lipoprotein concentrations in adults: analysis of published data*

Variable	Light smokers			Moderate smokers			Heavy smokers		
	No of studies	Mean (SE) Z score*	% Difference from value in non-smokers	No of studies	Mean (SE) Z score*	% Difference from value in non-smokers	No of studies	Mean (SE) Z score*	% Difference from value in non-smokers
Total cholesterol†	19	0·115 (0·017)	1·8	13	0·250 (0·016)	4·3	23	0·254 (0·012)	4·5
Triglycerides†	11	0·217 (0·027)	10·7	6	0·232 (0·029)	11·5	14	0·355 (0·029)	18·0
Very low density lipoprotein cholesterol†	2	0·057 (0·152)	7·2	1	0·736 (0·176)	44·4	2	0·566 (0·158)	39·0
Low density lipoprotein cholesterol†	3	−0·038 (0·101)	−1·1	2	0·032 (0·113)	1·4	4	0·677 (0·090)	11·0
High density lipoprotein cholesterol†	16	−0·173 (0·014)	−4·6	9	−0·261 (0·016)	−6·3	17	−0·357 (0·021)	−8·9
Apolipoprotein AI†	3	−0·226 (0·029)	−3·7				4	−0·318 (0·046)	−5·7

*See appendix for description of calculations.
†Linear test of trend, p<0·001.

social differences smokers might have a different diet from non-smokers and thus have altered lipid concentrations, but whether this would vary systematically with the amount smoked is unlikely unless such dietary differences were due to some physiological change such as altered perception of taste. In as much as the dietary changes would be caused by exposure to cigarette smoke the relation between smoking and serum lipid concentrations may, therefore, be considered causal. Studies on animals allow the effects of smoking to be studied independent of diet. Hojnacki *et al* studied the effects of cigarette smoking on lipoprotein compositions in pigeons under controlled dietary conditions.[60] Their results show that cigarette smoking can mediate changes in the composition of circulating lipoprotein in these birds independent of changes induced by dietary cholesterol and saturated fat. As further evidence in support of a causal relation lipid and lipoprotein concentrations in ex-smokers are either the same as those found in non-smokers or are intermediate between concentrations in smokers and non-smokers.[5 11 15 24 27 31-35 42 43 47 51 52 56] In addition, one longitudinal study showed that high density lipoprotein cholesterol and apolipoprotein AI concentrations return towards concentrations seen in non-smokers in people in the process of stopping smoking.[61]

In support of these clinical observations Brischetto *et al*[11] proposed a mechanism to explain the link between smoking and some of the observed changes in serum lipid and lipoprotein concentrations: (*a*) nicotine stimulates the release of adrenaline by the adrenal cortex, leading to the increased serum concentrations of free fatty acid observed in smokers[58]; (*b*) free fatty acid is a well known stimulant of hepatic secretion of very low density lipoprotein and hence triglyceride[59]; and (*c*) high density lipoprotein concentrations vary inversely with very low density lipoprotein concentrations in serum. Complementary to this mechanism is the finding that free fatty acid also stimulates hepatic synthesis and secretion of cholesterol.[62]

Cigarette smoking is reported to be associated with an average 70% increase in the risk of death from coronary artery disease.[63] In calculating this figure the surgeon general took into account all age groups. The excess risk of coronary artery disease associated with smoking is, however, relatively higher among younger than older adults.[63] To date sufficient data on prospective risk to allow the calculation of meaningful risk estimates are available only for serum cholesterol: a 1% increase in serum cholesterol concentration is associated with at least a 2% increase in the risk of coronary artery disease.[64 65] The 3·0% mean increase in serum cholesterol concentrations identified among all current smokers in the present study would therefore be associated with an estimated 6·0% higher absolute risk of coronary artery disease with a range of 3·6-9·0% higher absolute risk for light to heavy cigarette smoking. According to the present estimates, at least 9% of the total excess relative risk of coronary heart disease in current smokers could be accounted for by increased serum cholesterol concentrations. A further proportion of this excess risk is likely to be accounted for by changes in the other lipid and lipoprotein variables, but this cannot be quantified until their association with the risk of coronary artery disease is better defined prospectively.

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Appendix

Differences between smokers and non-smokers for each variable v were expressed as a proportion of the pooled standard deviation (Z score) with:

$$Z_v = \frac{\bar{v}_{ns} - \bar{v}_s}{SD_{pool}}$$

where $\bar{v}_{ns}$ and $\bar{v}_s$ are the mean values of the variable of interest in non-smokers and smokers, respectively. SD_{pool} is the pooled standard deviation for the smoking and non-smoking subgroups and was calculated for each study as:

$$SD_{pool} = \left[\frac{(N_{ns}-1)SD_{ns}^2 + (N_s-1)SD_s^2}{N_{ns}+N_s-2} \right]^{1/2}$$

where N_{ns} and N_s are the number of study subjects and S_{ns} and S_s are the standard deviations for non-smokers and smokers, respectively.

To obtain the overall estimate of the Z score for variable v each study estimate of Z_v was weighted by W_i (the reciprocal of the standard error of Z_v) squared.

$$W_i = \left[\frac{1}{N_{ns}} + \frac{1}{N_s} \right]^{-1}$$

Thus the overall weighted estimate for each variable v was:

$$\bar{Z}_v = \frac{\sum_{i=1}^{N} Z_{vi} W_i}{\sum_{i=1}^{N} W_i}$$

The test statistic used was:

$$t = \frac{\bar{Z}_v}{\left[\frac{1}{N_{ns}} + \frac{1}{N_s} \right]^{1/2}}$$

The percentage difference between smokers and non-smokers for each variable v in a given study was:

$$DIFF_v = \frac{(\bar{v}_{ns} - \bar{v}_s)\,100}{\bar{v}_{ns}}$$

To test for a dose response between smoking and the variable of interest the four categories of smoking non-, light, moderate, and heavy were assigned the numbers 0, 10, 20, and 30 respectively as an estimate of the number of cigarettes smoked and were regressed as described by Greenland[66] with a linear model with weighting as described above.

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ONE HUNDRED YEARS AGO

Before the New York Act directing that the death sentence shall in future be carried out by submitting the convict to a discharge of electricity could be enforced, it was necessary that the experiments should be repeated before the officials of the prisons service. After the rapid and painless character of the death had been demonstrated on dogs, four calves, each weighing about as much as a man, were killed, a current of 800 volts being used for fifteen seconds. Finally, a horse, weighing 800 pounds, was killed by a current of 1,000 volts, applied for fifteen seconds. All the animals, it is stated, died instantaneously, without pain or struggle. Bills drafted on the same lines as the New York Act are now, it is said, before the Legislatures of Alabama, Illinois, Ohio, and Missouri. (*British Medical Journal* 1889;i:788)